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What's new in heart failure? December 2024

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Introduction

This issue of the *European Journal of Heart Failure* features pioneering research addressing some of the most critical challenges in heart failure (HF) management. From the latest findings of the European Society of Cardiology (ESC) HF III Registry, investigating the real-world implementation of guideline-directed medical therapy (GDMT), to emerging evidence on HF subtypes such as HF with improved ejection fraction (HFimpEF) and HF with preserved ejection fraction (HFpEF). A notable study investigates the link between left ventricular (LV) volume and exercise capacity in HFpEF, shedding light on a unique phenotype. Other contributions include an exploration of HFpEF in adults with repaired coarctation of the aorta (COA) and novel use of multi-parametric cardiovascular magnetic resonance (CMR) for risk stratification in dilated cardiomyopathy with mildly reduced ejection fraction (DCMmrEF). The issue also provides a comprehensive review of chronic Chagas cardiomyopathy (CCC), a severe HF phenotype with global implications (*Figure 1*).

Packed with actionable insights and thought-provoking studies, this issue is a must-read for specialists dedicated to advancing HF care.

Insights from the ESC EURObservational Research Programme Heart Failure III Registry on guideline adherence and therapy optimization across Europe

The first analysis of the ESC HF III Registry provides a comprehensive overview of contemporary HF characteristics and management in ESC-affiliated countries.[1] This registry includes data collected between November 2018 and December 2020 from 10 162 patients across 41 countries, offering a robust snapshot of current HF care. This analysis serves as a critical resource for understanding variations in HF care by ejection fraction category, care setting (acute vs. outpatient), and HF origin (*de novo* vs. pre-existing). Additionally, it gives important insights into the adoption of GDMT in a real-world setting.

Heart failure with reduced ejection fraction (HFrEF) was the most prevalent form of HF (57%), followed by HFpEF (26%) and HF with mildly reduced ejection fraction (HFmrEF, 17%). GDMT was fairly well implemented among patients with HFrEF, with usage rates of 89% for renin–angiotensin system inhibitors (RASi), 29% for angiotensin receptor–neprilysin inhibitors (ARNi), 92% for beta-blockers, and 78% for mineralocorticoid receptor antagonists (MRA). GDMT implementation in HFmrEF was 89% for RASi, 10% for ARNi, 90% for beta-blockers, and 64% for MRA.

Despite being guideline-recommended since 2016,[2] ARNi adoption remains limited, likely due to challenges such as high costs, limited prescriber familiarity, and delays in the adoption of novel therapies. GDMT use in HFpEF was 77% for RASi, 3% for ARNi, 80% for beta-blockers, and 48% for MRA.

By presenting detailed data on patient characteristics and GDMT use, the ESC HF III Registry provides essential guidance for clinicians, researchers, and healthcare policymakers aiming to close the gap between guideline recommendations and real-world practice. Overall, implementation of GDMT is at a high level, with greater percentage use of GDMT medications than in most other large registries and cohorts and an improvement since the previous ESC HF Long-Term Registry, but these results emphasize the need for wider implementation of ARNi.[3,4] The present study, conducted in 2018–2020, cannot meaningfully assess sodium–glucose cotransporter 2 inhibitor (SGLT2i) use, as they were only beginning to emerge as a foundation therapy for HF during this period, but very recent data suggest that SGLT2i implementation has been more rapid than ARNi.[5]

Heart failure with improved ejection fraction: exploring predictors and outcomes

Cao *et al.*[6] delved into the clinical landscape of (HFimpEF), a distinct nosologic entity defined as an EF increase of ≥10 points to

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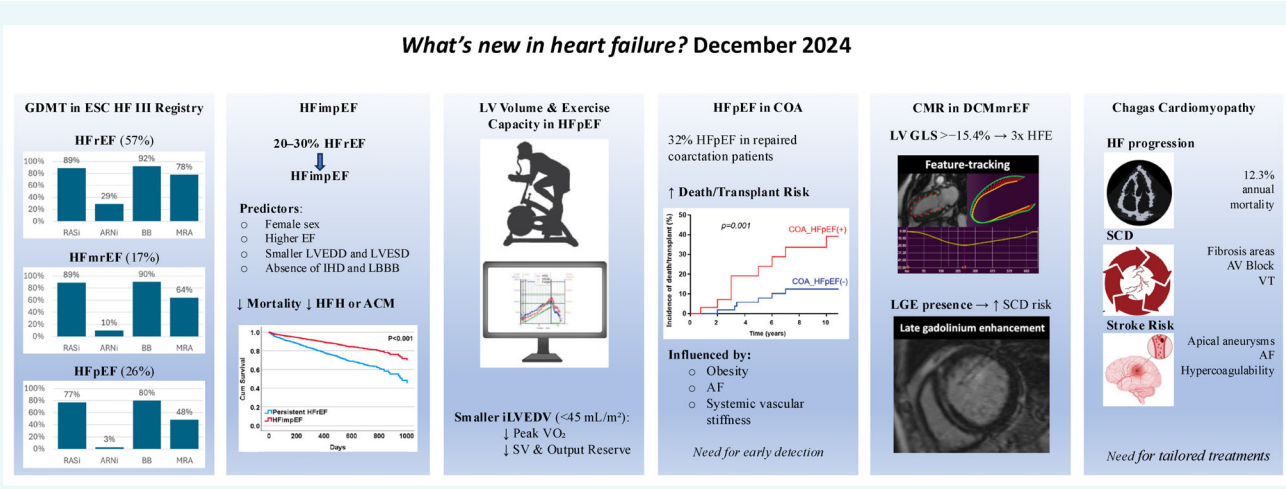

Figure 1 Key messages from latest heart failure studies. ACM, all-cause mortality; AF, atrial fibrillation; ARNi, angiotensin receptor–neprilysin inhibitor; AV, atrioventricular; BB, beta-blocker; CCC, chronic Chagas cardiomyopathy; CMR, cardiovascular magnetic resonance; COA, coarctation of the aorta; DCMmrEF, dilated cardiomyopathy with mildly reduced ejection fraction; EF, ejection fraction; ESC, European Society of Cardiology; GDMT, guideline-directed medical therapy; HF, heart failure; HFE, heart failure events; HFH, heart failure hospitalization; HFimpEF, heart failure with improved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IHD, ischaemic heart disease; iLVEDV, indexed left ventricular end-diastolic volume; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor; SCD, sudden cardiac death; SV, stroke volume; VO_2, oxygen consumption; VT, ventricular tachycardia.

>40%.[7] Leveraging data from the European BIOSTAT-CHF study, which had a median follow-up duration of 21 months (interquartile range [IQR] 15–27 months) and the multinational ASIAN-HF registry, the authors report that approximately 20–30% of patients with HFrEF transitioned to HFimpEF within 9–12 months. This transition was associated with better outcomes, including reduced all-cause mortality (hazard ratio [HR] 0.52, 95% confidence interval [CI] 0.28–0.97 in BIOSTAT-CHF; HR 0.40, 95% CI 0.18–0.89 in ASIAN-HF) and lower rates of the composite endpoint of all-cause mortality or new HF hospitalization (HR 0.46, 95% CI 0.30–0.70 in BIOSTAT-CHF; HR 0.29, 95% CI 0.17–0.48 in ASIAN-HF).[6,8,9]

The study identified five independent predictors of HFimpEF common to both cohorts: female sex, absence of ischaemic heart disease, higher baseline LV ejection fraction (LVEF), smaller LV end-diastolic diameter, and smaller LV end-systolic diameter. Absence of left bundle branch block, while not one of the initial five independent predictors, was later incorporated into a predictive model. This model demonstrated quite high accuracy, with an area under the curve (AUC) of 0.77 in BIOSTAT-CHF, to stratify patients likely to achieve HFimpEF.

The transition to HFimpEF was accompanied by favourable changes in symptoms and biomarkers like N-terminal pro-B-type natriuretic peptide (NT-proBNP).[7] In BIOSTAT-CHF, crude mortality rates among patients with HFimpEF were nearly halved compared to persistent HFrEF (7.2% vs. 14.4%, $p = 0.018$). These findings were validated in ASIAN-HF, demonstrating the global applicability of these predictors and outcomes.

The study emphasizes the importance of early identification of HFimpEF and represents a shift from the traditional 'one-size-fits-all' approach in HF management. From a practical perspective, early identification of HFimpEF may enable more individualized treatment strategies, where low-risk patients (HFimpEF) may benefit from less intensive follow-up, while high-risk patients (persistent HFrEF) require closer monitoring and therapeutic optimization. However, the study has several limitations, including survivor bias, differences in genetic background (Caucasian vs. Asian populations), and limitations in standard HF therapies between 2010 and 2015, the period during which both studies were conducted.

Unveiling the link between left ventricular volume and exercise capacity in heart failure with preserved ejection fraction

Smaller LV end-diastolic volume index (LVEDVi) has emerged as a potential predictor of reduced exercise capacity in patients with HFpEF.[10,11] In a prospective study of 133 HFpEF outpatients from a specialized HF clinic in Spain, who underwent cardiopulmonary exercise testing and echocardiography on the same day, smaller LVEDVi was significantly associated with lower peak oxygen consumption (peakVO_2) ($p = 0.0001$). Data were validated in a cohort of 82 patients with HFpEF from San Paolo Hospital, Milan, Italy

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($p = 0.004$). Patients with LVEDVi <45 ml/m^2, a cutoff corresponding to the median of the study derivation cohort, exhibited a median peakVO_2 of 10 ml/kg/min compared to 11 ml/kg/min in those with LVEDVi ≥45 ml/m^2 ($p = 0.028$). Additionally, individuals with reduced stroke volume (SVi <30 ml/m^2) and smaller LVEDVi had markedly worse exercise capacity, underscoring the critical role of cardiac output reserve during physical activity. Independent predictors of smaller LVEDVi included female sex, current or previous atrial fibrillation and continuous variables of higher body mass index and higher LVEF.[12]

The association between smaller LVEDVi and diminished exercise tolerance is multifactorial. The reduced LV cavity size limits the stroke volume increase during exercise, thereby decreasing cardiac output reserve. This relationship was particularly pronounced in patients with a higher ratio between left atrial (LA) and LV volumes, indicative of disproportionate LA enlargement relative to LV size. However, the study was not designed to directly measure cardiac output reserve or stroke volume increase during exercise, making these proposed mechanisms speculative.

An elevated ratio between LA and LV volumes may reflect increased LV filling pressures, contributing to exercise-induced pulmonary hypertension.[13] Interestingly, an inverted U-shaped relationship between LVEF and peakVO_2 was observed, with supranormal LVEF associated with reduced functional capacity, potentially due to stiff ventricles and impaired diastolic reserve.

These findings highlight the importance of LV cavity size in determining functional capacity in HFpEF and provide a rationale for incorporating LV volume metrics into future clinical trials and therapeutic strategies. Patients with HFpEF who have smaller LV cavity sizes represent a distinct phenotype that may require tailored therapeutic approaches. For example, down-titration of negative chronotropic medications or strategies promoting modest eccentric remodelling, such as tailored pacing therapies, may enhance functional capacity in this subgroup. Emerging data from randomized clinical trials such as PRESERVE-HR and myPACE suggest that personalized interventions, such as withdrawal of beta-blockers and rate-adaptive pacing, may offer substantial benefits in these patients, particularly those with concurrent chronotropic incompetence or supranormal LVEF. In PRESERVE-HR, the benefit of beta-blocker withdrawal was greatest among patients with lower LV end-systolic volume index. Meanwhile, in myPACE, although chronotropic incompetence is common among patients with HFpEF, it was not the primary focus. However, rate-adaptive pacing was active in most patients to treat this condition.[14,15]

Heart failure with preserved ejection fraction: a common complication in patients with repaired coarctation of the aorta

Egbe *et al.*[16] explored the prevalence and impact of HFpEF in adults with repaired COA, a congenital condition often associated with long-term cardiovascular remodelling. In a retrospective analysis of 99 adult patients with repaired COA who underwent right heart catheterization at a single-centre in the United States, 32% were found to have HFpEF, defined as dyspnoea on effort, LVEF ≥50% and elevated pulmonary artery wedge pressure at rest (>15 mmHg). Importantly, HFpEF was associated with significantly worse haemodynamic and structural parameters, including impaired pulmonary arterial compliance (PAC) and total arterial arterial compliance (TAC), as well as a higher risk of death or heart transplant (adjusted HR 1.68, $p = 0.02$).[16]

Heart failure with preserved ejection fraction correlated with obesity (adjusted odds ratio [OR] 4.15, $p = 0.02$) and atrial fibrillation (adjusted OR 3.13, $p = 0.05$), along with greater vascular dysfunction evidenced by decreased PAC index (adjusted OR 0.36 per 1 ml/mmHg × m^2, $p < 0.001$) and TAC index (adjusted OR 0.12 per 1 ml/mmHg × m^2, $p < 0.001$). Notably, systemic vascular stiffness, an often-overlooked element of COA pathophysiology, emerged as a significant determinant of HFpEF in these patients. Patients with HFpEF also demonstrated elevated right atrial and pulmonary pressures, higher NT-proBNP levels and reduced right ventricular-to-pulmonary artery coupling compared to those without HFpEF. The 10-year cumulative incidence of all-cause death or heart transplantation was 39% in patients with COA and HFpEF, significantly higher than the 12% observed in those with COA without HFpEF ($p = 0.001$). The accompanying editorial emphasizes the importance of recognizing HFpEF as a significant complication in patients with repaired COA, highlighting the chronic effects of vascular dysfunction and afterload increase as key drivers of disease progression.[17] The authors underscore the need for prevention or early detection of HFpEF in the COA population, including aggressive control of hypertension and obesity, as well as timely intervention for atrial fibrillation and residual COA.[18,19] Additionally, further research is needed to explore therapeutic strategies such as pharmacological interventions (e.g. SGLT2i and glucagon-like peptide-1 receptor agonists) and surgical measures to mitigate vascular stiffness and reduce risks associated with HFpEF. Given the young median age of this cohort (38 years), the potential for long-term benefit is substantial.

Multi-parametric cardiovascular magnetic resonance stratifies risk of heart failure and sudden cardiac death in dilated cardiomyopathy with mildly reduced ejection fraction

Heart failure associated with DCMmrEF represents a unique clinical subset characterized by a LVEF that lies between the reduced and normal range. While these patients often exhibit fewer symptoms and generally better long-term outcomes compared to those with more severe HF phenotypes, a significant subset is at risk of progressive HF or sudden cardiac death (SCD). Identifying these high-risk individuals remains a clinical challenge.

This prospective study, conducted at a single UK referral centre and its hospital network, assessed the role of CMR in stratifying

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the risk of HF progression and SCD in 355 patients with DCMmrEF (median age 54 years, 60.8% men, median LVEF 49%).[20] During a median follow-up of 7.8 years, 9% experienced HF events, and 5% suffered SCD or aborted SCD (aSCD). LV global longitudinal strain (GLS), derived through feature-tracking CMR, was independently associated with HF events when analysed as a continuous variable (per % HR 1.10, 95% CI 1.00–1.21, $p = 0.045$) or dichotomized at $> -15.4\%$ (HR 2.70, 95% CI 1.30–5.94, $p = 0.008$). Conversely, the presence of late gadolinium enhancement (LGE) was not associated with HF events (HR 1.49, 95% CI 0.73–3.01, $p = 0.270$), but significantly predicted SCD/aSCD (HR 3.58, 95% CI 1.39–9.23, $p = 0.008$). However, a key limitation is the lack of LGE quantification. Quantifying the extent of LGE could have provided additional insights into its prognostic value and the interplay between fibrosis and other markers, such as GLS. LVEF did not predict either HF or SCD events.

Patients with LV GLS $> -15.4\%$ had a higher cumulative incidence of HF events, with a 5-year HF rate of 13.5% compared to 3.2% in those with LV GLS $\leq -15.4\%$. By contrast, LGE-positive patients exhibited a 5-year SCD/aSCD rate of 3.7% versus 1.3% for LGE-negative patients. The study highlights the complementary roles of LV GLS and LGE and underscores the additive value of GLS to LVEF in risk prediction: indeed, LV GLS predicts HF episodes, while LGE identifies patients at elevated arrhythmic risk. These findings suggest that multi-parametric CMR offers a clinically valuable approach to risk stratification in DCMmrEF.

Chronic Chagas cardiomyopathy: unmasking a three-headed monster

Chronic Chagas cardiomyopathy, the most severe manifestation of *Trypanosoma cruzi* infection, is notable for its disproportionately high morbidity and mortality compared to other HF aetiologies. Traditionally endemic to Latin America, CCC is increasingly reported in non-endemic regions, including Europe and North America, due to migration and climate change, which expand the natural habitat of *Triatominae* vectors. A review paper delves into the 'three-headed monster' driving this outcome: progressive HF, SCD, and stroke.[21] HF progression results from parasite-induced myocardial damage and inflammation, causing diffuse fibrosis, ventricular remodelling and microvascular dysfunction.[22–24] The annual mortality rate for HF in stages C and D is estimated at 12.3%.[22] SCD arises from ventricular arrhythmias due to myocardial fibrosis, conduction abnormalities and autonomic dysfunction, with transmural fibrosis on CMR emerging as a key predictor.[25,26] Stroke risk is nearly double as compared to other HF aetiologies and is driven by apical aneurysms, atrial fibrillation and systemic hypercoagulability, leading to cardioembolic events.[27–29]

Despite advances in understanding CCC's pathophysiology, significant therapeutic gaps remain. Current HF management strategies are largely extrapolated from other aetiologies, leaving the specific needs of CCC insufficiently addressed.[30] The ongoing PARACHUTE-HF randomized trial (NCT04023227), designed to compare sacubitril/valsartan with enalapril in approximately 900 patients with CCC, represents a promising initiative focused on tailored interventions for this unique cardiomyopathy.[31–33] Emerging therapies targeting transforming growth factor-β signalling or employing mesenchymal stem cells show promise in pre-clinical studies, but encounter significant translational challenges.[34,35] Additionally, CCC often affects vulnerable populations, with limited access to specialized care and advanced therapies. These disparities contribute to the higher prevalence of advanced disease at diagnosis and worse outcomes.[36,37]

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